UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/535,509 | 05/18/2005 | Alcardo Koverech | 4865-47 | 7229 |

23117 7590 01/29/2009
NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

| EXAMINER | |
|---|---|
| BETTON, TIMOTHY E | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1617 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 01/29/2009 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/535,509 | KOVERECH ET AL. | |
| | Examiner | Art Unit | |
| | TIMOTHY E. BETTON | 1617 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *13 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *10-12 and 14-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-12 and 14-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

Applicants' Remarks filed on 13 November 2008 have been acknowledged and duly made of record.

The essence of applicants remarks are directed to the discussion held with regard to said case on 12 November 2008.

Principally, applicants' further assert the disorders listed in claim 10 for which there was acceptable enablement; those disorders not falling within this group have been excluded from claim 10. In addition, claim 10 has been revised to identify the subject as a patient diagnosed with andropause. Considering the evidence of record in this application including the extensive materials provided in Dr. Koverech's evidentiary declaration made May 13, 2008 as well as the application itself, it is respectfully submitted that claim 10 and the claims dependent from it are fully enabled and compliant with 35 USC § 112, first paragraph. The claims as above amended are also submitted to be patentable over the prior art cited in the current Official Action and discussed on pages 3-8 for the reasons of record including pages 5-8 of the Amendment and response of May 15, 2008 which pages are incorporated by reference herein.

Applicants request at this juncture is considered but is not found persuasive. Instant claim 10 is with issue because of the reasonable interpretation of broadness to the claim. The Examiner duly acknowledges the request amendments to instant claim 10. However, the claim is not constructed in such a way as to convey that these symptoms as disclosed are treatable based on a patient being diagnosed with andropause exclusively.

Principally, claim 10 discloses limitations that are not clearly distinguished as causes of the condition, *andropause.* Also, it is not determined to what extent these disease are caused by a patient diagnosed with andropause because of the limitation *comprising* which may be interpreted broadly.

Thus, applicants' arguments and remarks are considered but are not found persuasive for the reasons already made of record.

Thus, the rejections of record are maintained.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 10-12 and 14-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cavazza (USPN 4,474,812) (hereinafter Cavazza ('812)) and Cavazza (USPN 6,245,378) (hereinafter Cavazza ('378)) and De Felice (USPN 3,830,931 in view of De Simone (USPN 6,037, 373) and Xiu (USPN 6,399,116 B1).

Cavazza ('812) teaches a novel therapeutic use of L-carnitine and a pharmaceutical L-carnitine-comprising composition [...], whose oral or parenteral administration to elderly subjects brings about an improvement in the biochemical and behavioral parameters peculiar to senility (abstract only).

Cavazza ('812) teaches an embodiment drawn to L- carnitine which teaches the inventive objective of the claimed invention. Though Cavazza teaches embodiments drawn to treatment for senility in association with old-age, Cavazza teaches embodiments which to the skilled artisan would make instant claims 10-12 and 14-18 obvious.

Specifically, Cavazza teaches uses of L-carnitine [which] are already known. For instance, **L-carnitine has been used in the cardiovascular field in the treatment of acute and chronic myocardial ischaemia, angina pectoris, cardiac arrhythmias and insufficiency. In nephrology, L-carnitine has been administered to chronic uraemic patients who are subjected to regular haemodialysis treatment with a view to counteracting muscular asthenia and the onset of muscular cramps. Further therapeutic uses are the restoration of the HDL/LDL+VLDL ratio to normal and in total parenteral nutrition.**

It is, therefore, unexpected and surprising that, by orally or parenterally administering L-carnitine **to elderly subjects, an improvement in the biochemical and behavioral parameters** peculiar to senility, is brought about.

Although the daily dose to be administered depends on the age, weight and general condition of the elderly subject, utilizing sound professional judgment, it has been found that, generally, from about 10 to about 30 mg of L-carnitine/kg of body weight/day or an equivalent amount of a pharmacologically acceptable salt thereof, is a suitable dose.

L-carnitine is compounded into the pharmaceutical compositions by using the usual excipients, diluents and adjuvant agents which are well-known in pharmaceutical technology for preparing orally and parenterally administrable compositions. An extensive list of such

excipients and adjuvant agents as well as the methods for preparing solid and liquid oral unit dosage forms such as tablets, capsules, solutions, syrups and the like and fluid injectable forms such as sterile solutions, is disclosed in the U.S. Pat. No. 3,830,931 to De Felice.

It has also been found that a pharmaceutical composition in unit dosage form which is particularly suited for the foregoing therapeutic uses comprises from about 500 to about 1,000 mg of L-carnitine.

Several experiments were carried out, some of which are here in below described. The relevant results are also indicated.

Cavazza ('812) additionally teach the study of the effects of L-carnitine administration on some biochemical and behavioural parameters in old male rats.

Accordingly, Cavazza ('378) teaches a nutritional supplement for facilitating the adaptation of skeletal muscle in individuals undergoing programs of strenuous exercise and counteracting defatigation and weariness in asthenic individuals is disclosed, which comprises a combination of L-camitine, acetyl L-camitine and propionyl L-carnitine as basic active ingredients. Optional ingredients comprise isovaleryl L-carnitine, branched-chained aminoacids and creatine and/or phosphocreatine (abstract only).

Cavazza ('378) teaches an extensive embodiment of the indications for L-carnitine (column 2, lines 1-67).

Cavazza ('378) teaches mixtures, combinations and ratio strengths of acetyl and propionyl L-carnitine formulations which encompass the limitations of the instant claims (column 3, lines 64-67; column 4, lines 1-20).

The skilled artisan would instantly recognize that many of the disorders and disease states are conditions common among geriatric patients.

De Felice further confirms a well-established use of l-carnitine and carnitine derivatives among geriatric patients (please see Cases 1-12, columns 4-8).

The Cavazza references and De Felice do not specifically teach treatments for hormone disorders comprising andropause.

However, De Simone does teach L-acetyl carnitine and L-propionyl carnitine for the treatment of diseases that are related to the ageing subject (e.g. arthritis, asthenia, osteoporosis, etc) (abstract only).

De Simone also teaches an embodiment directed to specific salts of the carnitine formulation (column 2, lines 8-16).

None of the references above directly teach a formulation for the administration of decreased testosterone or a decreased libido.

However, Xiu does teach Rhodiola, preferably Rhodiola crenulata, to treat various conditions and diseases in mammals. Rhodiola crenulata is a Tibetan herb which has been discovered to have highly useful and beneficial properties heretofore unknown. Rhodiola crenulata is especially preferred to enhance blood oxygen levels, to enhance working capacity and endurance, to enhance memory and concentration, to enhance cardiac and cardiovascular function, to provide antioxidant effects, to protect against oxidation, **to modulate testosterone and estradiol levels**, to modulate sleep, and **to enhance sexuability, such as improve sexual performance.**

Xiu teaches a preferred embodiment drawn to the administration of carnitines in combination with Rhodiola crenulata. This adequately encompasses the inventive objective and subject matter limitation disclosed in instant claim 1. Particularly, instant claim 1 cites a method for the treatment of disorders caused by andropause ***comprising*** administering [...].

Specifically, Xiu teach andropause as disorder indicated for treatment.

Testosterone is considered to be a male virilizing hormone. Its effects include maintenance of muscle and bone mass, improving and/or enhancing sexual function and psychological well being among others. As males grow older, especially after the age of 35, a slow decline in testosterone levels is observed which is accompanied by symptoms that have been associated with the condition known as "andropause". Symptoms of andropause include lethargy, depression, lack of sexual desire and function, and loss of muscle mass and strength. Increasing testosterone levels therefore can be useful to treat any of the mentioned conditions. Additionally, increasing testosterone levels can be useful in treating certain types of breast cancer in women (column 4, lines 55-67).

Thus, it would have been prima facie obvious to the skilled artisan at the time of invention to incorporate with or combine together the methods and teachings of Cavazza, De Felice, De Simone and Xiu.

The Cavazza references teach methods and intended uses for L-carnitines and derivatives thereof. Cavazza ('812) specifically teaches the study of the effects of L-carnitine administration on some biochemical and behavioral parameters in old male rats. The inventive objective in view of the claimed invention is drawn to elderly male subjects. De Felice and De Simone provide the primary motivation to combine via the administration of L-carnitine for an array of diseases

associated with ageing. Accordingly, Xui teaches embodiments of andropause being treated preferably by L-carnitines, L-carnitine mixtures, and compositions thereof.

In consideration of the above, the skilled artisan would instantly recognize motivation in the incorporating together of the references as explained in obviousness over claimed invention.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-12 and 14-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment for erectile dysfunction, does not reasonably provide enablement for treatment of all disorders caused by andropause. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

> There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:
>
> (A) The breadth of the claims;
> (B) The nature of the invention;
> (C) The state of the prior art;
> (D) The level of one of ordinary skill;
> (E) The level of predictability in the art;
> (F) The amount of direction provided by the inventor;
> (G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The central issue of the scope of enablement is drawn to several factors as outlined above. Specifically, the state of the prior art, nature of the invention, and the quantity of experimentation are of a certain significance in view of the inventive objective of claimed invention.

The state of the art is addressed by Tan, Robert State of the Art Anti-Aging Practice: Diagnostic Difficulties of the Andropause (copyright 2003), Associate Professor, Department of Family Medicine at the University of Texas/ Houston, pp. 473-482, (abstract, page 473) [that] Even before contemplating hormonal replacement for men, practitioners should be certain of a diagnosis of low testosterone causing andropause-related symptoms. This is partly because accurate diagnosis may be confounded due to factors such as clinical depression, hypothyroidism, anemia, alcoholism, psychological states, and side effects of medications.

There is undeniable evidence that bioavailable testosterone declines with age. However, there are variations in testosterone measures based on timing and method used for quantification, and this will be explored in this chapter. There are limitations of blood and saliva measurements of testosterone, and andropause should be diagnosed only in conjunction with a clinical assessment, as it is a complex syndrome.

The decline of testosterone leads to hypogonadism, which can present with symptoms in older men. However, like in the menopause, not all older men present with transitional symptoms as they enter the andropause. The long-term effects of andropause in men may be similar to menopause, as decline in androgens can affect libido, musculoskeletal, cardiac, and cognitive functions. In addition, in contrast to menopause, men in andropause do not necessarily

suffer from infertility as sperm production continues. The evidence of the impact of low testosterone on the aging male's physiology will be examined. Androgen supplementation in the form of testosterone may be effective for some individuals who are symptomatic. At the present time, is no routine recommendation for androgen replacement in all males. The practitioner should select his patient carefully based on symptoms and biochemical evidence of hypogonadism. Monitoring of side effects of androgens, including changes in prostate, hemoglobin levels, etc., is mandatory (abstract only).

Thus, Tan cites evidence that the state of the art with regard to andropause is developing which causes the scope of applicants invention to be unclear in view of what the applicant is claiming based on treatment for all symptoms of andropause.

Accordingly, the nature of the invention which is drawn from the state of the art possesses a scope of enablement when the invention (the method of treatment) sufficiently supports and suggests that there was reasonable possession of the claimed invention. The declaration does not support possession for all that the applicants claim. The nature of the art necessitates incorporation of some form of correlative data in conjunction with related guidance and direction as to what gives the invention a clear scope of enablement.

Further, the quantity of experimentation needed to use the invention based on the content of the disclosure is deficient. Experimentation is drawn to correlative and cumulative data drawn to erectile function disorders but no where in the declaration does it provide support for all the disorder limitations of claim 10. On the face of Tan reference *supra* in view of applicants' declaration, it would not be apparent to one of ordinary skill that all such disorders caused by andropause may be treated. Further it would not be apparent to the one of skill that the applicant

had possession of the invention based on the deficiency in the declaration to resolve all disclosed limitations of claim 10.

Thus, unpredictability is high. It's relatedness to a lack of sufficient and relevant quantified experimentation is found in the current invention. Applicants disclose nothing to the contrary to reasonably rebut evidentiary disclosure of Tan. Even in the alternate, in which case Tan is superceded by evidence to points to an improved state of the art, the scope of applicants' scope of enablement is still deficient.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy E. Betton whose telephone number is (571) 272-9922. The examiner can normally be reached on Monday-Friday 8:30a - 5:00p.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197

(toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shengjun Wang/

Primary Examiner, Art Unit 1617